

side by side	Query	Hit Count	Set Name result set
	<i>DB=PGPB,USPT; PLUR=YES; OP=ADJ</i>		
<u>L6</u>	(antibod\$)same(ctla4 or 'ctla-4') and (antibod\$) same (toxin or toxin)same (conjugate\$ or immunotoxin\$)	125	<u>L6</u>
<u>L5</u>	(antibod\$)same(ctla4 or 'ctla-4') and (antibod\$) same (toxin or toxin)	210	<u>L5</u>
	<i>DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ</i>		
<u>L4</u>	(antibod\$)same(ctla4 or 'ctla-4')same (toxin or toxin)	18	<u>L4</u>
<u>L3</u>	L2 and (antibod\$)same (25 or 26 or 29)	3	<u>L3</u>
<u>L2</u>	L1 and (ctla\$)		

Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 20030108549 A1

L3: Entry 1 of 3

File: PGPB

Jun 12, 2003

PGPUB-DOCUMENT-NUMBER: 20030108549
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030108549 A1

TITLE: Methods and compositions for modulating interleukin-21 receptor activity

PUBLICATION-DATE: June 12, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carter, Laura	Medford	MA	US	
Carreno, Beatriz	Acton	MA	US	
Lowe, Leslie D.	Sudbury	MA	US	
Whitters, Matthew J.	Hudson	MA	US	
Dunussi, Kyri	Belmont	MA	US	
Collins, Mary	Natick	MA	US	
Ma, Margery	Roxbury	MA	US	
Young, Deborah A.	Melrose	MA	US	
Witek, JoAnn S.	Acton	MA	US	
Larsen, Glenn	Sudbury	MA	US	
Kasaian, Marion T.	Charlestown	MA	US	
Donaldson, Debra D.	Medford	MA	US	
Unger, Michelle	Chapel Hill	NC	US	

US-CL-CURRENT: 424/145.1; 514/251, 514/291, 514/406

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw. De
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☐ 2. Document ID: US 20020176855 A1

L3: Entry 2 of 3

File: PGPB

Nov 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020176855
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020176855 A1

TITLE: HUMANIZED IMMUNOGLOBULIN REACTIVE WITH B7-2 AND METHODS OF TREATMENT THEREWITH

PUBLICATION-DATE: November 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
CO, MAN SUNG	CUPERTINO	CA	US	

VASQUEZ, MAXIMILIANO	PALO ALTO	CA	US
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GOLDMAN, SAMUEL	ACTON	MA	US
GRAY, GARY S.	BROOKLINE	MA	US
KNIGHT, ANDREA	HAMPTON	NH	US
O'HARA, DENISE	READING	MA	US
RUP, BONITA	READING	MA	US
VELDMAN, GEERTRUIDA M.	SUDBURY	MA	US

US-CL-CURRENT: 424/133.1; 424/141.1, 424/143.1, 424/144.1, 424/153.1, 424/173.1,
435/252.3, 435/320.1, 435/326, 435/328, 435/334, 435/343, 435/346, 435/440,
435/455, 435/69.6, 530/387.3, 530/388.1, 530/388.22, 530/388.73, 536/23.1,
536/23.4, 536/23.53

Full	Title	Classification	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	ABC	Draw D
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☐ 3. Document ID: US 20020039581 A1

L3: Entry 3 of 3

File: PGPB

Apr 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020039581
 PGPUB-FILING-TYPE: new
 DOCUMENT-IDENTIFIER: US 20020039581 A1

TITLE: Antibodies against CTLA4 and uses therefor

PUBLICATION-DATE: April 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
<u>Carreno</u> , Beatriz M.	Acton	MA	US	
Wood, Clive	Boston	MA	US	
Turner, Katherine	Acton	MA	US	
Collins, Mary	Natick	MA	US	
Gray, Gary S.	Brookline	MA	US	
Morris, Donna	Salem	NH	US	
O'Hara, Denise	Reading	MA	US	
Hinton, Paul R.	Fremont	CA	US	
Tsurushita, Naoya	Palo Alto	CA	US	

US-CL-CURRENT: 424/178.1; 530/391.7

Full	Title	Classification	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	ABC	Draw D
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Term	Documents
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"26"	3720600
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"29"	2208799
29S	394
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ANTIBOD	969
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ANTIBODAY	1
(L2 AND (ANTIBOD\$)SAME (25 OR 26 OR 29)).PGPB,USPT,EPAB,JPAB,DWPI.	3

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Jun 12, 2003

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Carter, Laura	Medford	MA	US	
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Kasaian, Marion T.	Charlestown	MA	US	
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Unger, Michelle	Chapel Hill	NC	US	

US-CL-CURRENT: 424/145.1; 514/251, 514/291, 514/406

Pub	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	FIGS	Draw D.
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☐ 2. Document ID: US 20020176855 A1

L3: Entry 2 of 3

File: PGPB

Nov 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020176855
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020176855 A1

TITLE: HUMANIZED IMMUNOGLOBULIN REACTIVE WITH B7-2 AND METHODS OF TREATMENT THEREWITH

PUBLICATION-DATE: November 28, 2002

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CO, MAN SUNG	CUPERTINO	CA	US	

VASQUEZ, MAXIMILIANO	PALO ALTO	CA	US
CARRENO, BEATRIZ	ACTON	MA	US
CELNIKER, ABBIE CHERYL	NEWTON	MA	US
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GOLDMAN, SAMUEL	ACTON	MA	US
GRAY, GARY S.	BROOKLINE	MA	US
KNIGHT, ANDREA	HAMPTON	NH	US
O'HARA, DENISE	READING	MA	US
RUP, BONITA	READING	MA	US
VELDMAN, GEERTRUIDA M.	SUDBURY	MA	US

US-CL-CURRENT: [424/133.1](#); [424/141.1](#), [424/143.1](#), [424/144.1](#), [424/153.1](#), [424/173.1](#),
[435/252.3](#), [435/320.1](#), [435/326](#), [435/328](#), [435/334](#), [435/343](#), [435/346](#), [435/440](#),
[435/455](#), [435/69.6](#), [530/387.3](#), [530/388.1](#), [530/388.22](#), [530/388.73](#), [536/23.1](#),
[536/23.4](#), [536/23.53](#)

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☐ 3. Document ID: US 20020039581 A1

L3: Entry 3 of 3

File: PGPB

Apr 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020039581
 PGPUB-FILING-TYPE: new
 DOCUMENT-IDENTIFIER: US 20020039581 A1

TITLE: Antibodies against CTLA4 and uses therefor

PUBLICATION-DATE: April 4, 2002

INVENTOR-INFORMATION:

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<u>Carreno</u> , Beatriz M.	Acton	MA	US	
Wood, Clive	Boston	MA	US	
Turner, Katherine	Acton	MA	US	
Collins, Mary	Natick	MA	US	
Gray, Gary S.	Brookline	MA	US	
Morris, Donna	Salem	NH	US	
O'Hara, Denise	Reading	MA	US	
Hinton, Paul R.	Fremont	CA	US	
Tsurushita, Naoya	Palo Alto	CA	US	

US-CL-CURRENT: [424/178.1](#); [530/391.7](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	ABC	Draw D
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DOCUMENT-IDENTIFIER: US 6242586 B1

TITLE: Mammalian cell surface antigens: related reagents

Brief Summary Text (4):

The activation of resting T cells is critical to most immune responses and allows these cells to exert their regulatory or effector capabilities. See Paul (ed; 1993) Fundamental Immunology 3d ed., Raven Press, N.Y. Increased adhesion between T cells and antigen presenting cells (APC) or other forms of primary stimuli, e.g., immobilized monoclonal antibodies (mAb), can potentiate the T-cell receptor signals. T-cell activation and T cell expansion depends upon engagement of the T-cell receptor (TCR) and co-stimulatory signals provided by accessory cells. See, e.g., Jenkins and Johnson (1993) Curr. Opin. Immunol. 5:361-367; Bierer and Hahn (1993) Semin. Immunol. 5:249-261; June, et al. (1990) Immunol. Today 11:211-216; and Jenkins (1994) Immunity 1:443-446. A major, and well-studied, co-stimulatory interaction for T cells involves either CD28 or CTLA-4 on T cells with either B7 or B70 (Jenkins (1994) Immunity 1:443-446). Recent studies on CD28 deficient mice (Shahinian, et al. (1993) Science 261:609-612; Green, et al. (1994) Immunity 1:501-508) and CTLA-4 immunoglobulin expressing transgenic mice (Ronchese, et al. (1994) J. Exp. Med. 179:809-817) have revealed deficiencies in some T-cell responses though these mice have normal primary immune responses and normal CTL responses to lymphocytic choriomeningitis virus and vesicular stomatitis virus. As a result, both these studies conclude that other co-stimulatory molecules must be supporting T-cell function. However, identification of these molecules which mediate distinct costimulatory signals has been difficult.

Brief Summary Text (63):

Further, the antibodies, including antigen binding fragments, of this invention can be potent antagonists that bind to the antigen and inhibit functional binding or inhibit the ability of a binding partner to elicit a biological response. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides so that when the antibody binds to antigen, a cell expressing it, e.g., on its surface, is killed. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker, and may effect drug targeting.

Brief Summary Text (105):

499E9, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, topical, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Pa.; Avis, et al. (eds.) (1993) Pharmaceutical Dosage

Forms: Parenteral Medications, Dekker, N.Y.; Lieberman, et al. (eds.) (1990)
Pharmaceutical Dosage Forms: Tablets, Dekker, N.Y.; and Lieberman, et al. (eds.)
(1990) Pharmaceutical Dosage Forms: Disterse Systems, Dekker, N.Y. The therapy of
this invention may be combined with or used in association with other agents, e.g.,
other modulators of T cell activation, e.g., CD40, CD40 ligand, CD28, CTLA-4, B7,
B70, SLAM, T cell receptor signaling entities, or their respective antagonists.

DOCUMENT-IDENTIFIER: US 6632926 B1

TITLE: Antibody variants

Detailed Description Text (40):

Preferred molecular targets for antibodies encompassed by the present invention include CD proteins such as CD3, CD4, CD8, CD19, CD20 and CD34; members of the ErbB receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor; cell adhesion molecules such as LFA-1, Mac1, p150,95, VLA-4, ICAM-1, VCAM and .alpha.v.beta.3 integrin including either alpha or beta subunits thereof (e.g. anti-CD11a, anti-CD18 or anti-CD11b antibodies); growth factors such as VEGF; IgE; blood group antigens; flk2/flt3 receptor; obesity (OB) receptor; mpl receptor; CTLA-4; protein C etc.

Detailed Description Text (115):

The invention also pertains to immunoconjugates comprising the antibody described herein conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g. (e.g. an enzymatically active toxin of bacterial, fungal, plant or animal origin, or or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Summary of Invention Paragraph:

[0051] Anti-human CTLA-4 human monoclonal antibodies of the invention, or antigen binding portions thereof (e.g., Fab), can be derivatized or linked to another functional molecule, e.g., another peptide or protein (e.g., an Fab' fragment). For example, an antibody or antigen-binding portion of the invention can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities. For example, the human sequence anti-CTLA-4 antibody, or antigen binding fragment thereof, can be conjugated to a therapeutic moiety, e.g., a cytotoxic drug, an enzymatically active toxin, or a fragment thereof, a radioisotope, or a small molecule anti-cancer drug. The antibodies of the invention can also be conjugated to cytotoxic pharmaceuticals, e.g., radiolabeled with a cytotoxic agents, such as, e.g., .sup.131I (e.g. Shen (1997) Cancer 80(12 Suppl):2553-2557), copper-67 (e.g., Deshpande (1988) J. Nucl. Med. 29:217-225) or, e.g., conjugation to the ribosome inactivating protein gelonin (e.g., Boyle (1996) J. of Immunol. 18:221-230).

Detail Description Paragraph:

[0251] Other methods of the invention are used to treat patients that have been exposed to particular toxins or pathogens. Similar to its application to tumors as discussed above, antibody mediated CTLA-4 blockade can be used alone, or as an adjuvant, in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self-antigens. CTLA-4 blockade has been shown to be effective in the acute phase of infections of *Nippostrongylus brasiliensis* (McCoy, K. et al. (1997) 186(2); 183-187) and *Leishmania donovani* (Murphy, M. et al. (1998) J. Immunol. 161:4153-4160). Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, *Leishmania*, *Staphylococcus aureus*, *Pseudomonas Aeruginosa*. CTLA-4 blockade is particularly useful against established infections by agents such as HIV that present altered antigens over the course of the infections. These novel epitopes are recognized as foreign at the time of anti-human CTLA-4 administration, thus provoking a strong T cell response that is not dampened by negative signals through CTLA-4.

Summary of Invention Paragraph:

[0003] B7-1 also interacts with the T cell CTLA4 receptor. Its signaling is complex, but one component provides a negative feedback signal, causing the T cell to attenuate the CD28 signal. In the absence of this signal for a long period of time, rampant T cell proliferation and effector cell activation continues. However, shorter term intervention can be beneficial by leading to a more vigorous immune response. For example, when the interaction of B7-1 (and B7-2) is blocked with antibodies to CTLA4 increased rejection of tumors has been found. When this feedback regulation malfunctions, autoimmune diseases and lymphoproliferation (refs) can result. For example, when the CTLA4 and B7-1 interaction is blocked with a soluble CTLA4Ig, allograft tolerance and resistance to autoimmune diseases have been observed.

Summary of Invention Paragraph:

[0007] Clearly, costimulatory signaling through T cell surface receptors plays an important role in maintaining balance in the immune system. Systems with a predominance of activatory signals, such as the costimulatory signaling between CD28 and B7-1, can lead to autoimmunity and inflammation. Immune systems with a predominance of inhibitory signals, such as the costimulatory signaling between CTLA4 and are less able to challenge infected cells or cancer cells. Isolating new molecules involved in costimulatory signaling is highly desirable for studying the biological signal(s) transduced via the receptor. Additionally, identifying such molecules provides a means of regulating and treating diseased states associated with autoimmunity, inflammation and infection. For example, engaging a molecule that stimulates inhibitory or negative signaling with an agonistic antibody or signaling partner can be used to downregulate a cell function in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present. On the other hand, using an antagonistic antibody specific for a molecule that stimulates negative signaling, or using a soluble form of the molecule to block signaling, can activate the specific immune function in disease states associated with suppressed immune function. Conversely, engaging a molecule that stimulates positive signaling with an agonistic antibody can be used to upregulate the effect of that molecule's signaling.

Summary of Invention Paragraph:

[0056] As discussed above, when various tissues were analyzed for mRNA for B7L-1, transcripts were detected in human bone marrow derived CD34+ derived dendritic cells and peripheral blood derived dendritic cells, B cells after stimulation with CD40L, brain and mouse splenic dendritic cells CD40L stimulated splenic B cells and brain. Because of the restricted expression pattern of B7L-1, antibodies to B7L-1 can be used to identify, isolate, and purify potent antigen presenting cells, including dendritic cells and CD40 ligand activated B cells. Additionally, the presence and level of mRNA for B7L-1 can be exploited to determine the purity of bone marrow derived and blood derived dendritic cell preparations. Other uses of antibodies to B7L-1 molecules include targeting antigens to myeloid dendritic cells or eliminating myeloid dendritic cells with anti-B7L-1 antibody mediated depletion or with an conjugate of a toxin and the antibody.

Summary of Invention Paragraph:

[0058] One embodiment of the present invention is directed to a method of treating disorders mediated by the interaction of B7L-1 and a binding partner and involves administering B7L-1 to a mammal having the disorder. B7L-1 polypeptides of the invention can be formulated according to known methods used to prepare pharmaceutically useful compositions. B7L-1 can be combined in admixture, either as the sole active material or with other known active materials, with pharmaceutically suitable

diluents (e.g., Tris-HCl, acetate, phosphate), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), emulsifiers, solubilizers, adjuvants and/or carriers. Suitable carriers and their formulations are described in Remington's Pharmaceutical Sciences, 16th ed. 1980, Mack Publishing Co. In addition, such compositions can contain B7L-1 complexed with polyethylene glycol (PEG), metal ions, or incorporated into polymeric compounds such as polyacetic acid, polyglycolic acid, hydrogels, etc., or incorporated into liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts or spheroblasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance of B7L-1. B7L-1 can also be conjugated to antibodies against tissue-specific receptors, ligands or antigens, or coupled to ligands of tissue-specific receptors. For tumor cells on which LDCAM is found, B7L-1 may be conjugated to a toxin whereby B7L-1 is used to deliver the toxin to the specific cell site.

Summary of Invention Paragraph:

[0010] Immunotoxins comprising an antibody linked to a toxin have been proposed for the prophylaxis and/or treatment of organ transplant rejection and induction of immunological tolerance. For example, a chemically conjugated diphtheria immunotoxin directed against rhesus CD3. epsilon., i.e. FN18-DT390, has been used in primate models of allograft tolerance and also in primate islet concordant xenograft models, see Knechtle et al. (1997) Transplantation 63:1, Neville et al. (1996) J. Immunother. 19: 85; Thomas et al. (1997) Transplantation 64: 124; Contreras et al. (1998) Transplantation 65: 1159-1169. Additionally, a chemically coupled Pseudomonas immunotoxin, LMB-1 B3(Lys)-PE38, has been used in clinical trials against advanced solid tumors, Pai, L. H. and I. Pastan, Curr. Top. Microbiol. Immunol. 234:83-96 (1998). However, product heterogeneity is a significant practical difficulty associated with chemically conjugated immunotoxins.

Summary of Invention Paragraph:

[0011] A single chain recombinant immunotoxin comprising the variable region of an anti-CD3 antibody, UCHT-1 and a diphtheria toxin, has been proposed as a therapeutic agent, see WO 96/32137, WO 98/39363. However, early vaccination of the general population against diphtheria raises concerns about pre-existing antibodies to the toxin in many patients. Alternately, a recombinant immunotoxin comprising anti-Tac linked to PE38 is also proposed as a prophylaxis and treatment against organ transplantation and autoimmune disease, see Mavroudis et al. (1996). Bone Marrow Transplant. 17: 793.

Detail Description Paragraph:

[0064] A single chain immunotoxin according to the invention comprises such a single chain antibody fragment. The toxin component is preferably fused to the CD3-binding domain(s), optionally via a linker linker peptide, but may also exist as a separate polypeptide chain linked via one or more disulfide bonds to the chain containing the CD3-binding domain.

Detail Description Paragraph:

[0123] The dimerized immunotoxin constructs depicted in FIGS. 16A, C, D, E and F comprise two (or more) chains. The construct depicted in FIG. 16B is a divalent single chain immunotoxin. The molecules shown in FIG. 16E are full length recombinantly prepared antibodies linked to a toxin. The construct of FIG. 16F is a recombinantly prepared F(ab').sub.2 fragment (i.e. comprising a dimer of two pairs of chains) linked to toxin.

Detail Description Paragraph:

[0198] The immunotoxins can be administered in vivo either alone or in combination with other pharmaceutical agents effective in treating acute or chronic transplant rejection including cyclosporin A, cyclosporin G, rapamycin, 40-O-2-hydroxyethyl-substituted rapamycin (RAD), FK-506, mycophenolic acid, mycophenolate mofetil (MMF), cyclophosphamide, azathioprene, brequinar, leflunamide, mizoribine, deoxyspergualines, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY 720), corticosteroids (e.g., methotrexate, prednisolone, methylprednisolone, dexamethasone), or other immunomodulatory compounds (e.g., CTLA4-Ig); anti-LFA-1 or anti-ICAM antibodies, or other antibodies that prevent co-stimulation of T cells, for example antibodies to leukocyte receptors or their ligands (e.g., antibodies to MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45, CD58, CD152 (CTLA-4), or CD 154 (CD40 ligand).

Detail Description Paragraph:

[0246] Depletion of T-cell numbers by 2 logs, by a chemically conjugated immunotoxin comprised of an anti-rhesus CD3 monoclonal antibody conjugated to a cell binding domain-deleted form of diphtheria toxin, has been shown to be associated with transplantation tolerance to renal allografts in rhesus monkeys (Thomas et al., 1997, Transplantation 64:124-135; Knechtle et al., 1997, Transplantation 63:1-6).

DOCUMENT-IDENTIFIER: US 5994511 A

**** See image for Certificate of Correction ****

TITLE: Anti-IgE antibodies and methods of improving polypeptides

Detailed Description Text (160):

Preferred molecular targets for antibodies encompassed by the present invention include CD proteins such as CD3, CD4, CD8, CD19, CD20 and CD34; members of the ErbB receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor; cell adhesion molecules such as LFA-1, Mac12, p150,95, VLA-4, ICAM-1, VCAM and .alpha.v/.beta.3 integrin including either a or b subunits thereof (e.g. anti-CD11a, anti-CD18 or anti-CD11b antibodies); growth factors such as VEGF; IgE; blood group antigens; flk2/flk3 receptor; obesity (OB) receptor; mpl receptor; CTLA-4; protein C etc. An especially preferred target is IgE.

Detailed Description Text (239):

The invention also pertains to immunoconjugates comprising the antibody described herein conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g. and enzymatically active toxin of bacterial, fungal, plant or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Detail Description Paragraph:

[0098] The present invention is further intended to include derivatives of antibodies or fragments thereof which retain a desired functional property, e.g., the ability to inhibit an interaction between gc chain and a gc chain ligand. Antibody derivatives include chimeric molecules, humanized molecules, molecules with reduced effector functions, bispecific molecules, and conjugates of antibodies or antibody portions with toxins or radionuclides. An antibody, or fragment thereof, produced in a non-human subject can be recognized to varying degrees as foreign when the antibody is administered into a human subject and an immune response against the antibody may be generated in the subject. One approach for minimizing or eliminating this problem is to produce chimeric, humanized, or primatized antibody derivatives, i.e., antibody molecules comprising portions which are derived from non-human antibodies (e.g., derived from mice or monkeys) and portions which are derived from human antibodies. Chimeric antibody molecules can include, for example, the variable region from an antibody of a mouse, rat or other species, with human constant regions. a variety of approaches for making chimeric antibodies have been described. (See, for example, Morrison et al., Proc. Natl. Acad. Sci. U.S.A. 81,6851 (1985); Takeda et al., Nature 314, 452 (1985), Cabilly et al., U.S. Pat. No. 4,816,567; Boss et al., U.S. Pat. No. 4,816,397; Tanaguchi et al., EP 171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B.) In a further modification, humanized antibodies have only the hypervariable domains of the variable region of non-human origin and have other parts of the variable region of the antibody, especially the conserved framework regions of the antigen-binding, domain, of human origin. Such humanized antibodies can be made by any of several techniques known in the art, (e.g., Teng et al., Proc. Natl. Acad. Sci. U.S.A. 80, 7308-7312 (1983); Olsson et al., Meth. Enzymol., 92, 3-16 (1982)), and are preferably made according to the teaching of PCT Publication WO 92/06193 or EP 0239400. Humanized antibodies can be commercially produced by, for example, Scotgen Limited, 2 Holly Road, Twickenham, Middlesex, Great Britain.

Detail Description Paragraph:

[0175] In this embodiment of the invention, unresponsiveness of a T cell to an antigen is maintained by contacting the T cell with an agent, such as a gc chain blocking antibody, which inhibits stimulation of the T cell through gc chain-encompassing cytokine receptors. Agents which inhibit stimulation by binding to gc chain may result in complete or partial inhibition, so long as it is sufficient to maintain T cell unresponsiveness as defined herein. In one embodiment of the invention, T cell unresponsiveness is maintained to an antigen on an allogeneic or xenogeneic cell. Accordingly, the method of the invention can be used to treat a subject who is a recipient of the allogeneic or xenogeneic cell, for example an organ transplant recipient, and is useful for inhibiting either rejection of transplanted tissue or graft vs. host disease in a subject. In another embodiment of the invention, T cell unresponsiveness is maintained to an autoantigen or to an allergen. Accordingly, the method of the invention can be used to treat a subject suffering from an autoimmune or an allergic disease, and is useful for alleviating the symptoms of those disorders associated with an inappropriate or undesired immune response. The gc chain blocking agent employed to maintain T cell unresponsiveness in these therapeutic situations may be administered subsequent to application of the agent used to induce T cell unresponsiveness. Where the agent used to induce T cell unresponsiveness is an agent other than a gc chain blocking antibody, such as CTLA-4 Ig, the gc chain blocking agent can be administered simultaneously with the inducing agent.

DOCUMENT-IDENTIFIER: US 20020160000 A1

TITLE: PD-1, a receptor for B7-4, and uses therefor

Detail Description Paragraph:

[0063] Inhibitory receptors that bind to costimulatory molecules have also been identified on immune cells. Activation of CTLA4, for example, transmits a negative signal to a T cell. Engagement of CTLA4 inhibits IL-2 production and can induce cell cycle arrest (Krummel and Allison (1996) J. Exp. Med. 183:2533). In addition, mice that lack CTLA4 develop lymphoproliferative disease (Tivol et al. (1995) Immunity 3:541; Waterhouse et al. (1995) Science 270:985). The blockade of CTLA4 with antibodies may remove an inhibitory signal, whereas aggregation of CTLA4 with antibody transmits an inhibitory signal. Therefore, depending upon the receptor to which a costimulatory molecule binds (i.e., a costimulatory receptor such as CD28 or an inhibitory receptor such as CTLA4), certain B7 molecules including can promote promote T cell costimulation or inhibition.

Detail Description Paragraph:

[0065] The instant discovery that PD-1 binds to B7-4 places PD-1 in a family of inhibitory receptors with CTLA4. While engagement of a costimulatory receptor results in a costimulatory signal in an immune cell, engagement of an inhibitory receptor, e.g., CTLA4 or PD-1 (for example by crosslinking or by aggregation), leads leads to the transmission of an inhibitory signal in an immune cell, resulting in downmodulation of immune cell responses and/or in immune cell anergy. While transmission of an inhibitory signal leads to downmodulation in immune cell responses (and a resulting downmodulation in the overall immune response), the prevention of an inhibitory signal (e.g., by using a non-activating antibody against PD-1) in immune cells leads to upmodulation of immune cell responses (and a resulting upmodulation of an immune response).

Detail Description Paragraph:

[0087] As used herein, the term "inhibitory signal" refers to a signal transmitted via an inhibitory receptor (e.g., CTLA4 or PD-1) for a molecule on a immune cell. Such a signal antagonizes a signal via an activating receptor (e.g., via a TCR, CD3, BCR, or Fc molecule) and can result in, e.g., inhibition of second messenger generation; an inhibition of proliferation; an inhibition of effector function in the immune cell, e.g., reduced phagocytosis, reduced antibody production, reduced cellular cytotoxicity, the failure of the immune cell to produce mediators, (such as cytokines (e.g., IL-2) and/or mediators of allergic responses); or the development of anergy.

Detail Description Paragraph:

[0090] Preferred B7 polypeptides are capable of providing costimulatory or inhibitory signals to immune cells to thereby promote or inhibit immune cell responses. For example, when bound to a costimulatory receptor, B7-4 can induce costimulation of immune cells or can inhibit immune cell costimulation, e.g., when present in soluble form. When bound to an inhibitory receptor, B7-4 molecules can transmit an inhibitory signal to an immune cell. Preferred B7 family members include B7-1, B7-2, B7-3 (recognized by the antibody BB-1), B7h, and B7-4 and soluble fragments or derivatives thereof. In one embodiment, B7 family members bind to one or more receptors on an immune cell, e.g., CTLA4, CD28, ICOS, PD-1 and/or other receptors, and, depending on the receptor, have the ability to transmit an inhibitory signal or a costimulatory signal to an immune cell, preferably a T cell.

Detail Description Paragraph:

[0263] Likewise, the PD-1 pathway can also be stimulated by the use of an agent to thereby downmodulate the immune response. Inhibition of the interaction of B7-4 with a stimulatory receptor on an immune cell (e.g., by using a soluble form of PD-1 and/or CTLA4) or activation of PD-1 (e.g., using an activating antibody which cross-links PD-1) may provide negative signals to immune cells.

Detail Description Paragraph:

[0264] In one embodiment of the invention, an activating antibody used to stimulate PD-1 activity is a bispecific antibody. For example, such an antibody can comprise a PD-1 binding site and another binding site which targets a cell surface receptor on an immune cell, e.g., on a T cell, a B cell, or a myeloid cell. In one embodiment, such an antibody, in addition to comprising a PD-1 binding site can further comprise a binding site which binds to a molecule which is in proximity to an activating or inhibitory receptor, e.g., B-cell antigen receptor, a T-cell antigen receptor, or an Fc receptor in order to target the molecule to a specific cell population. For example, a CD3 antigen, a T-cell receptor chain, LFA-1, CD2, CTLA-4, immunoglobulin, B cell receptor, Ig alpha, Ig beta, CD22, or Fc receptor could be used. Such antibodies (or other bispecific agents) are art recognized and can be produced, e.g., as described herein. Selection of this second antigen for the bispecific antibody provides flexibility in selection of cell population to be targeted for inhibition.

Detail Description Paragraph:

[0268] In one embodiment, fusion proteins comprising a B7-4 first peptide fused to a second peptide having an activity of another B lymphocyte antigen (e.g., B7-1 or B7-2), can be used to block interaction of B7-4 with a costimulatory receptor on a immune cell to downmodulate immune responses. Alternatively, two separate peptides (for example, a B7-4 polypeptide with B7-2 and/or B7-1), or a combination of blocking antibodies (e.g., antibodies against a B7-4 polypeptide with anti-B7-2 and/or anti-B7-1 monoclonal antibodies) can be combined as a single composition or administered separately (simultaneously or sequentially) to downregulate immune cell mediated immune responses in a subject. Furthermore, a therapeutically active amount of one or more peptides having a B7-4 polypeptide activity, with B7-1 and/or B7-1 activity can be used in conjunction with other downmodulating reagents to influence immune responses. Examples of other immunomodulating reagents include antibodies that block a costimulatory signal, (e.g., against CD28, ICOS), antibodies that activate an inhibitory signal via CTLA4, and/or antibodies against other immune cell markers (e.g., against CD40, against CD40 ligand, or against cytokines), fusion proteins (e.g., CTLA4-Fc, PD-1-Fc), and immunosuppressive drugs, (e.g., rapamycin, cyclosporine A or FK506).

Detail Description Paragraph:

[0271] A wide variety of toxins are known that may be conjugated to polypeptides or antibodies of the invention. Examples include: numerous useful plant-, fungus- or even bacteria-derived toxins, which, by way of example, include various A chain toxins, particularly ricin A chain, ribosome inactivating proteins such as saporin or gelonin, alpha.-sarcin, aspergillin, restrictocin, ribonucleases such as placental ribonuclease, angiogenic, diphtheria toxin, and pseudomonas exotoxin, etc. A preferred toxin moiety for use in connection with the invention is toxin A chain which has been treated to modify or remove carbohydrate residues, deglycosylated A chain. (U.S. Pat. No. 5,776,427).

Detail Description Paragraph:

[0274] To achieve sufficient immunosuppression or tolerance in a subject, it may also be desirable to block the costimulatory function of other molecules. For example, it may be desirable to block the function of B7-1 and B7-4, B7-2 and B7-4, or B7-1 and B7-4 by administering a soluble form of a combination of peptides

having an activity of each of these antigens or blocking antibodies against these antigens (separately or together in a single composition) prior to or at the time of transplantation. Alternatively, it may be desirable to promote inhibitory activity of B7-4 or PD-1 and inhibit a costimulatory activity of B7-1 and/or B7-2. Other downmodulatory agents that can be used in connection with the downmodulatory methods of the invention include, for example, agents that transmit an inhibitory signal via CTLA4, soluble forms of CTLA4, antibodies that activate an inhibitory signal via CTLA4, blocking antibodies against other immune cell markers or soluble forms of other receptor ligand pairs (e.g., agents that disrupt the interaction between CD40 and CD40 ligand (e.g., anti CD40 ligand antibodies)), antibodies against cytokines, or immunosuppressive drugs. In another embodiment, a combination of at least two different B7-4 antibodies can be administered to achieve optimal blocking activity.

Detail Description Paragraph:

[0293] An in vitro immune cell costimulation assay as described above can also be used in a method for identifying novel cytokines which can be modulated by modulation of B7-4 and or PD-1. For example, where stimulation of the CD28/CTLA4 pathway seems to enhance IL-2 secretion, stimulation of the ICOS pathway seems to enhance IL-10 secretion (Hutloff et al. 199. Nature 397:263). If a particular activity induced upon costimulation, e.g., immune cell proliferation, cannot be inhibited by addition of blocking antibodies to known cytokines, the activity may result from the action of an unknown cytokine. Following costimulation, this cytokine can be purified from the media by conventional methods and its activity measured by its ability to induce immune cell proliferation.

Detail Description Paragraph:

[0401] The ability of COS cells expressing B7-4M to bind to various T cell receptors and antibodies was tested. FACS analysis of binding of CD28Ig, CTLA4-Ig, and control Ig by B7-4-transfected COS cells showed that neither CD28Ig nor CTLA4-Ig was bound by B7-4 (FIG. 8). The ability of COS cells expressing B7-4M to bind to IgG and murine ICOS-his fusion protein was also tested. No binding of human B7-4 to murine ICOS was detected (FIG. 9). As shown in FIG. 10, FACS analysis revealed binding of BB 1 (anti B7-1 and anti B7-3), but not IgM or 133 (anti-B7) antibodies to B7-4-transfected COS cells.

Detail Description Paragraph:

[0413] Antibody reactivity and specificity for B7-4 or PD-1 are assessed using an indirect enzyme-linked immunosorbent assay (ELISA). Several immunoglobulin superfamily molecules are tested as controls (e.g., CTLA4 and CD28) to analyze the antibody specificity of the antibody for B7-4 or PD-1. Antibodies having human variable regions which bind to B7-4 or PD-1 are detected by enzyme conjugates specific for human IgM and human IgG sub-classes with no cross reactivity to mouse immunoglobulin. Briefly, PVC microtiter plates are coated with B7-4 or PD-1 by coating wells overnight at 37.degree. C. with 5 .mu.g/mL B7-4 in PBS. Serum samples are diluted in PBS, 5% serum, 0.5% Tween-20 and are incubated in the wells for 1 hour at room temperature, followed by anti-human IgG Fc and IgG F(ab')-horseradish peroxidase or anti-human IgM Fc-horseradish peroxidase in the same diluent. After 1 hour at room temperature enzyme activity is assessed by addition of ABTS substrate (Sigma, St. Louis, Mo.) and read after 30 minutes at 415-490 .mu.m. In pre-immunization serum samples from the same mice, titers of human antibodies to the same target antigens are also tested.

Detail Description Paragraph:

[0419] In addition, an in situ assay of transfected COS cell monolayers was performed. Monolayers were probed with PD-1 Fc, CTLA4Fc or human IgG1 and binding was detected with a secondary antibody directed against the Fc portion and conjugated to alkaline phosphatase. Binding was visualized with chromogenic substrates 5-bromo-4-chloro-3-indolyl phosphate and nitro blue tetrazolium and light microscopy. In parallel, cells transfected with B7-4 were found to bind to

PD-1-Fc, and not CTLA4-Fc (human Ig gamma 1) or Flt4-Fc, the extracellular region of of murine Flt4 linked to human Ig gamma 1. In parallel, PD-1Fc did not bind the surface of mock-transfected, B7-1 or B7-2 transfected COS cells.

DOCUMENT-IDENTIFIER: US 20030044768 A1

TITLE: PD-1, a receptor for B7-4, and uses therefor

Detail Description Paragraph:

[0056] Inhibitory receptors that bind to costimulatory molecules have also been identified on immune cells. Activation of CTLA4, for example, transmits a negative signal to a T cell. Engagement of CTLA4 inhibits IL-2 production and can induce cell cycle arrest (Krummel and Allison (1996) J. Exp. Med. 183:2533). In addition, mice that lack CTLA4 develop lymphoproliferative disease (Tivol et al. (1995) Immunity 3:541; Waterhouse et al. (1995) Science 270:985). The blockade of CTLA4 with antibodies can block an inhibitory signal, whereas aggregation of CTLA4 with antibody transmits an inhibitory signal. Therefore, depending upon the receptor to which a costimulatory molecule binds (i.e., a costimulatory receptor such as CD28 or an inhibitory receptor such as CTLA4), certain B7 molecules including B7-4 can promote T cell costimulation or inhibition.

Detail Description Paragraph:

[0058] The instant discovery that PD-1 binds to B7-4 places PD-1 in a family of inhibitory receptors with CTLA4. While engagement (to produce activation) of a costimulatory receptor results in a costimulatory signal in an immune cell, engagement of an inhibitory receptor, e.g., CTLA4 or PD-1 (for example by crosslinking or by aggregation), leads to the transmission of an inhibitory signal in an immune cell, resulting in downmodulation of immune cell responses and/or in immune cell anergy. While transmission of an inhibitory signal leads to downmodulation in immune cell responses (and a resulting downmodulation in the overall immune response), the prevention of an inhibitory signal (e.g., by using a non-activating antibody against PD-1) in immune cells leads to upmodulation of immune cell responses (and a resulting upmodulation of an immune response).

Detail Description Paragraph:

[0082] As used herein, the term "inhibitory signal" refers to a signal transmitted via an inhibitory receptor (e.g., CTLA4 or PD-1) for a molecule on a immune cell. Such a signal antagonizes a signal produced by an activating receptor (e.g., via a TCR, CD3, BCR, or Fc molecule) and can result in, e.g., inhibition of second messenger generation; an inhibition of proliferation; an inhibition of effector function in the immune cell, e.g., reduced phagocytosis, reduced antibody production, reduced cellular cytotoxicity, the failure of the immune cell to produce mediators, (such as cytokines (e.g., IL-2) and/or mediators of allergic responses); or the development of anergy.

Detail Description Paragraph:

[0085] Preferred B7 polypeptides are capable of providing costimulatory or inhibitory signals to immune cells to thereby promote or inhibit immune cell responses. For example, when bound to a costimulatory receptor, B7-4 can induce costimulation of immune cells or can inhibit immune cell costimulation, e.g., when present in soluble form. When bound to an inhibitory receptor, B7-4 molecules can transmit an inhibitory signal to an immune cell. Preferred B7 family members include B7-1, B7-2, B7-3 (recognized by the antibody BB-1), B7h, and B7-4 and soluble fragments or derivatives thereof. In one embodiment, B7 family members bind to one or more receptors on an immune cell, e.g., CTLA4, CD28, ICOS, PD-1 and/or other receptors, and, depending on the receptor, have the ability to transmit an inhibitory signal or a costimulatory signal to an immune cell, preferably a T cell.

Detail Description Paragraph:

[0253] Likewise, the PD-1 pathway can also be stimulated by the use of an agent to thereby downmodulate the immune response. This is accomplished via inhibition of the interaction of B7-4 with a stimulatory receptor on an immune cell (e.g., by using a soluble form of PD-1 and/or CTLA4) or activation of PD-1 (e.g., using an activating antibody which cross-links PD-1) to provide negative signals to immune cells.

Detail Description Paragraph:

[0254] In one embodiment of the invention, an activating antibody used to stimulate PD-1 activity is a bispecific antibody. For example, such an antibody can comprise a PD-1 binding site and another binding site which targets a cell surface receptor on an immune cell, e.g., on a T cell, a B cell, or a myeloid cell. In one embodiment, such an antibody, in addition to comprising a PD-1 binding site can further comprise a binding site which binds to a molecule which is in proximity to an activating or inhibitory receptor, e.g., B-cell antigen receptor, a T-cell antigen receptor, or an Fc receptor in order to target the molecule to a specific cell population. For example, a CD3 antigen, a T-cell receptor chain, LFA-1, CD2, CTLA-4, immunoglobulin, B cell receptor, Ig alpha, Ig beta, CD22, or Fc receptor could be used. Such antibodies (or other bispecific agents) are art recognized and can be produced, e.g., as described herein. Selection of this second antigen for the bispecific antibody provides flexibility in selection of cell population to be targeted for inhibition.

Detail Description Paragraph:

[0258] In one embodiment, fusion proteins comprising a B7-4 first peptide fused to a second peptide having an activity of another B lymphocyte antigen (e.g., B7-1 or B7-2), can be used to block interaction of B7-4 with a costimulatory receptor on a immune cell to downmodulate immune responses. Alternatively, two separate peptides (for example, a B7-4 polypeptide with B7-2 and/or B7-1), or a combination of blocking antibodies (e.g., antibodies against a B7-4 polypeptide with anti-B7-2 and/or anti-B7-1 monoclonal antibodies) can be combined as a single composition or administered separately (simultaneously or sequentially) to downregulate immune cell mediated immune responses in a subject. Furthermore, a therapeutically active amount of one or more peptides having a B7-4 polypeptide activity, with B7-1 and/or B7-2 activity can be used in conjunction with other downmodulating reagents to influence immune responses. Examples of other immunomodulating reagents include antibodies that block a costimulatory signal, (e.g., against CD28, ICOS), antibodies that activate an inhibitory signal via CTLA4, and/or antibodies against other immune cell markers (e.g., against CD40, against CD40 ligand, or against cytokines), fusion proteins (e.g., CTLA4-Fc, PD-1-Fc), and immunosuppressive drugs, (e.g., rapamycin, cyclosporine A or FK506).

Detail Description Paragraph:

[0261] A wide variety of toxins are known that may be conjugated to polypeptides or antibodies of the invention. Examples include: numerous useful plant-, fungus- or even bacteria-derived toxins, which, by way of example, include various A chain toxins, particularly ricin A chain, ribosome inactivating proteins such as saporin or gelonin, alpha.- sarcin, aspergillin, restrictocin, ribonucleases such as placental ribonuclease, angiogenic, diphtheria toxin, and pseudomonas exotoxin, etc. A preferred toxin moiety for use in connection with the invention is toxin A chain which has been treated to modify or remove carbohydrate residues, deglycosylated A chain. (U.S. Pat. No. 5,776,427).

Detail Description Paragraph:

[0264] To achieve sufficient immunosuppression or tolerance in a subject, it may also be desirable to block the costimulatory function of other molecules. For example, it may be desirable to block the function of B7-1 and B7-4, B7-2 and B7-4,

or B7-1 and B7-2 and B7-4 by administering a soluble form of a combination of peptides having an activity of each of these antigens or blocking antibodies against these antigens (separately or together in a single composition) prior to or at the time of transplantation. Alternatively, it may be desirable to promote inhibitory activity of B7-4 or PD-1 and inhibit a costimulatory activity of B7-1 and/or B7-2. Other downmodulatory agents that can be used in connection with the downmodulatory methods of the invention include, for example, agents that transmit an inhibitory signal via CTLA4, soluble forms of CTLA4, antibodies that activate an inhibitory signal via CTLA4, blocking antibodies against other immune, cell markers or soluble forms of other receptor ligand pairs (e.g., agents that disrupt the interaction between CD40 and CD40 ligand (e.g., anti CD40 ligand antibodies)), antibodies against cytokines, or immunosuppressive drugs. In another embodiment, a combination of at least two different B7-4 antibodies can be administered to achieve optimal blocking activity.

Detail Description Paragraph:

[0284] An in vitro immune cell costimulation assay as described above can also be used in a method for identifying novel cytokines which can be modulated by modulation of B7-4 and or PD-1. For example, where stimulation of the CD28/CTLA4 pathway seems to enhance IL-2 secretion, stimulation of the ICOS pathway seems to enhance IL-10 secretion (Hutloff et al. 199. Nature 397:263). If a particular activity induced upon costimulation, e.g., immune cell proliferation, cannot be inhibited by addition of blocking antibodies to known cytokines, the activity may result from the action of an unknown cytokine. Following costimulation, this cytokine can be purified from the media by conventional methods and its activity measured by its ability to induce immune cell proliferation.

Detail Description Paragraph:

[0405] The ability of COS cells expressing B7-4M to bind to various T cell receptors and antibodies was tested. FACS analysis of binding of CD28Ig, CTLA4-Ig, and control Ig by B7-4-transfected COS cells showed that neither CD28Ig nor CTLA4-Ig was bound by B7-4 (FIG. 8). The ability of COS cells expressing B7-4M to bind to IgG and murine ICOS-his fusion protein was also tested. No binding of human B7-4 to murine ICOS was detected (FIG. 9). As shown in FIG. 10, FACS analysis revealed binding of BB1 (anti B7-1 and anti B7-3), but not IgM or 133 (anti-B7) antibodies to B7-4-transfected COS cells.

Detail Description Paragraph:

[0418] Antibody reactivity and specificity for B7-4 or PD-1 are assessed using an indirect enzyme-linked immunosorbent assay (ELISA). Several immunoglobulin superfamily molecules are tested as controls (e.g., CTLA4 and CD28) to analyze the antibody specificity of the antibody for B7-4 or PD-1. Antibodies having human variable regions which bind to B7-4 or PD-1 are detected by enzyme conjugates specific for human IgM and human IgG sub-classes with no cross reactivity to mouse immunoglobulin. Briefly, PVC microtiter plates are coated with B7-4 or PD-1 by coating wells overnight at 37.degree. C. with 5 .mu.g/mL B7-4 in PBS. Serum samples are diluted in PBS, 5% serum, 0.5% Tween-20 and are incubated in the wells for 1 hour at room temperature, followed by anti-human IgG Fc and IgG F(ab')-horseradish peroxidase or anti-human IgM Fc-horseradish peroxidase in the same diluent. After 1 hour at room temperature enzyme activity is assessed by addition of ABTS substrate (Sigma, St. Louis, Mo.) and read after 30 minutes at 415-490 nm. In pre-immunization serum samples from the same mice, titers of human antibodies to the same target antigens are also tested.

Detail Description Paragraph:

[0424] In addition, an in situ assay of transfected COS cell monolayers was performed. Monolayers were probed with PD-1Fc, CTLA4Fc or human IgG1 and binding was detected with a secondary antibody directed against the Fc portion and conjugated to alkaline phosphatase. Binding was visualized with chromogenic substrates 5-bromo-4-chloro-3-indolyl phosphate and nitro blue tetrazolium and

light microscopy. In parallel, cells transfected with B7-4 were found to bind to PD-1-Fc, and not CTLA4-Fc (human Ig gamma 1) or Flt4-Fc, the extracellular region of murine Flt4 linked to human Ig gamma 1. In parallel, PD-1Fc did not bind the surface of mock-transfected, B7-1 or B7-2 transfected COS cells.

DOCUMENT-IDENTIFIER: US 20030119076 A1

TITLE: B7-like polynucleotides, polypeptides, and antibodies

Summary of Invention Paragraph:

[0003] Costimulatory interactions between the B7 family ligands and their receptors play critical roles in the growth, differentiation and death of T cells. Engagement of the T cell costimulator CD28 by either specific antibodies or its natural ligands B7-1 and B7-2 increases antigen-specific proliferation of CD4+ T cells, enhances production of cytokines, induces maturation of CD8+ effector T cells, and promotes T cell survival (Chambers, C. A., et al., Curr. Opin. Immunol., 9:396-404 (1997); Lenschow, D. J., et al., Annu. Rev. Immunol., 14:233-58 (1996); Chen, L., et al., Immunol. Today, 14:483-86 (1993); Boise, L. H., et al., Curr. Opin. Immunol., 7:620-25 (1995)). Signaling through the homologous CTLA-4 receptor of B7-1 and B7-2 on activated T cells, however, is thought to deliver a negative signal that inhibits T cell proliferation, IL-2 production, and cell cycle progression (Krummel, M. F., et al., J. Exp. Med., 183:2533-540 (1996); Walunas, T. L., et al., J. Exp. Med., 183:2541-550 (1996)).

Detail Description Paragraph:

[0214] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

Detail Description Paragraph:

[0257] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

Detail Description Paragraph:

[0523] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to treat, diagnose, and/or prevent cancers or neoplasms including autoimmune cell or tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are described herein and include acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkins disease, non-Hodgkins

lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, plasmacytomas, multiple myeloma, Burkitt's lymphoma, and EBV-transformed diseases. In a preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent cancers and neoplasms. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent, acute myelogenous leukemia.

Detail Description Paragraph:

[0996] It has been reported that both CTLA-4 and ICOS can be induced to express on the surface of activated T cells, while CD28 expresses constitutively. Therefore, B7-H3 is a potential ligand for CTLA-4 and ICOS. To exclude this possibility, 293 cells were transfected with the plasmids encoding B7-H3, B7-H2, or B7-1 separately, and the cells were subsequently stained with anti-B7-H3 antibody, CTLA-4-Ig, and ICOS-Ig and subjected to FACS analysis. Anti-B7-H3 antibody specifically stained 293 cells transfected to express B7-H3, but not B7-1 and B7-H2, demonstrating that B7-H3 is expressed as a cell surface protein by transfection. Neither CTLA-4-Ig nor ICOS-Ig stained B7-H3/293 cells, while they can bind B7-1/293 and B7-H2/293 cells, respectively (FIG. 6B). Our results thus suggest that B7-H3 is a ligand for an inducible T cell receptor different from CTLA-4 and ICOS.

DOCUMENT-IDENTIFIER: US 20030171551 A1

TITLE: CHIMERIC ANTIBODY FUSION PROTEINS FOR THE RECRUITMENT AND STIMULATION OF AN ANTITUMOR IMMUNE RESPONSE

Summary of Invention Paragraph:

[0005] Although various different trials of monoclonal antibodies, antibody based conjugates and/or radioantibody have been performed, with limited success, results of these trials have highlighted obstacles to successful antibody therapy of human malignancy. Antibody opsonization generally does not result in direct cytotoxicity, due to poor fixation of complement and/or poor enlistment of antibody dependent cytotoxicity (ADCC) (Junghans, R. P. et al., "Antibody-Based Immunotherapies for Cancer," in Chabner et al., eds., Cancer Chemotherapy and Biotherapy, 2nd Ed., Philadelphia, Pa., 655-89 (1996); Schlom, J., "Antibodies in Cancer Therapy: Basic Principles of Monoclonal Antibodies," in DeVita et al., eds., Biologic Therapy of Cancer, New York: J. B. Lippincott Co., 464-81 (1991)). Strategies based on direct antibody-based killing (e.g. antibody-toxin conjugates such as antibody-ricin, or radiolabeled antibody strategies, e.g. sup.131I-Ab) require delivery to all tumor cells and are hampered by limited vascular permeability to proteins of 150 kd or greater (mw of IgG) and extravascular diffusion ability (Jain, R. K., "Transport of Molecules Across Tumor Vasculature," Cancer and Metastasis Reviews, 6:559-93 (1987); Jain, R. K., "Transport of Molecules in the Tumor Interstitium: A Review," Cancer Res., 47:3039-51 (1987); Jain, R. K., "Determinants of Tumor Blood Flow: A Review," Cancer Res., 48:2641-58 (1988); Jain, R. K., "Barriers to Drug Delivery in Solid Tumors," Sci. Amer., 1:58-65 (1994)). Elevated interstitial pressures within tumor masses due to absent/poorly organized lymphatics further impede delivery. Antibody (Ab) and cytokine activation of effector cells may be more effective than Ab alone (LeBerthon, B. L. et al., "Enhanced Tumor Uptake of Macromolecules Induced by a Novel Vasoactive IL-2 Immunoconjugate," Cancer Res., 51:2694 (1991); Hank, J. A. et al., "Augmentation of ADCC Following In vivo Therapy with Recombinant IL-2," Cancer Res., 50:5234-39 (1990)).

Detail Description Paragraph:

[0055] The molecular weight, the structural assembly between heavy and light chains, and the glycosylation pattern can be determined in the presence and absence of tunicamycin as performed for the anti DNS-B7.1 and IL-2 fusion proteins. Correct translation and folding of the B7.1 domain can be assessed using several methods. ELISA assays could be performed using a monoclonal antibody to B7.1, one such antibody is the BB-1 antibody to B7.1. Specificity and affinity of B7.1 binding to the costimulatory receptor(s) CTLA4 and CD28 is characterized by quantitative radioimmunoprecipitation with soluble CTLA4Ig and CD28Ig (CTLA4Ig from P. Linsley, and CD28Ig from Bristol-Meyers Squibb). CHO cell lines stably expressing either CD28 or B7.1 have been obtained from Dr. P. Linsley (Bristol-Meyers, Washington) (Linsley, P. S. et al., "Binding of the B Cell Activation Antigen B7 to CD28 Costimulates T Cell Proliferation and Interleukin 2 mRNA Accumulation," J Exp Med, 173:721 (1991), which is hereby incorporated by reference). CD28+CHO cells are used to measure binding of the B7.1 antibody fusion proteins by flow cytometry using FITC-labelled anti-human IgG.

Detail Description Paragraph:

[0061] The invention also provides a gene encoding the chimeric molecule. For example, one method of making the chimeric molecules is depicted in FIG. 2, in particular B7.1 and RANTES antibody fusion proteins specific for CEA and her2/neu. For each construct, the tumor specific fusion protein (e.g., anti-CEA/B7.1 or anti-CEA/RANTES), tumor specific antibodies lacking the fusion protein, and non-specific antibodies of the same structure can be compared. Vectors for the expression of antibodies

recognizing CEA and her2/neu are produced. Plasmids are also produced encoding variable regions for "humanized" 4D5 her2/neu specific antibody from Dr. Paul Carter of Genentech, (Carter, P., et al., "Humanization of an Anti-p185HER2 Antibody for Human Cancer Therapy," Proc Natl Acad Sci USA 89:4285 (1992), which is hereby incorporated by reference). PCR is used to modify the variable regions to make them suitable for use in the vectors. If needed, variable regions from additional hybridomas specific for her2/neu (ATCC) can be cloned. (Coloma, J. J., et al., "Novel Vectors for the Expression of Antibody Molecules Using Variable Regions Generated by PCR", Immunol. Methods, 152:89 (1992), which is hereby incorporated by reference). Variable regions so cloned are expressed as fusion protein using the expression vectors. Several versions of the B7.1 and RANTES antibody fusion proteins can be constructed. Initially, three different antibody fusion proteins are being studied. In a first version, B7.1 or RANTES is fused to the carboxy-terminus of the Ig heavy chain. In a second version, they are fused to the amino-terminus of IgG3 via a flexible linker to make the amino-terminus of either RANTES or B7.1 more available for ligand binding, since it has been shown to be crucial for the activity of both B7.1 (Guo, Y., et al., "Mutational Analysis and an Alternatively Spliced Product of B7 Defines its D28/CTLA4-Binding Site in Immunoglobulin C-like Domain" J Exp Med 181:1345 (1995), which is hereby incorporated by reference) and RANTES (Wells, T. N. C., et al. "Peptides from the Amino-Terminus of RANTES Cause Chemotaxis of Human T-Lymphocytes" Biochem Biophys Res Com 211:100 (1995), which is hereby incorporated by reference), while preserving the antigen binding site. In a third version, they are fused to the carboxy-terminus, but with the inclusion of a flexible linker at the fusion site in order to provide more flexibility to the fusion.

Detail Description Paragraph:

[0130] The expression vectors for the human IgG3 heavy and kappa light chains were previously described (Coloma, M. et al., "Novel Vectors for the Expression of Antibody Molecules Using Variable Regions Generated by Polymerase Chain Reaction," J Immunol Methods 152:89-104 (1992), which is hereby incorporated by reference). The variable domains of the anti-HER2/neu antibody were amplified by PCR from the plasmid pAK19 (kindly provided by P. Carter, Genentech Inc.) (Carter, P. et al., "High Level Escherichia Coli Expression and Production of a Bivalent Humanized Antibody Fragment," Biotechnology (10) 10:163-7 (1992), which is hereby incorporated by reference), and cloned into the corresponding heavy or light chain expression vectors to derive her2.IgG3. To construct a fusion antibody between her2.IgG3 and B7.1 (referred to as B7.her2.IgG3), the extracellular domain of human B7.1 was cloned at the 5'-end of the heavy chain variable region of her2.IgG3 (FIG. 10). A flexible (Ser-Gly.sub.4).sub.3 linker was provided at the fusion site of the recombinant fusion protein to facilitate correct folding of both antibody and B7.1 domains. B7.1 was expressed at the amino terminus of the heavy chain because B7.1 fused to the carboxyl terminus of the C.sub.H3 domain showed decreased affinity for CD28. These results are consistent with a critical role of the amino terminus of B7.1 in mediating its biological activity (Guo, Y. et al., "Mutational Analysis and an Alternatively Spliced Product of B7 Defines its CD28/CTLA4-Binding Site on Immunoglobulin C-Like Domain," J Exp Med 181:1345-1355 (1995), which is hereby incorporated by reference). The light chain and either the her2.IgG3 or B7.her2.IgG3 heavy chain expression vectors were cotransfected into Sp2/0 myeloma cells and stable transfectants secreting soluble proteins identified by ELISA.

Detail Description Paragraph:

[0158] The examples also show the construction and characterization of a fusion antibody in which the extracellular domain of the B7.1 costimulatory molecule was fused by genetic engineering to the amino terminus of the heavy chain of an anti-HER2/neu antibody. The IgG3 backbone was chosen for the antibody molecule since the extended hinge region of IgG3 would be expected to provide greater flexibility in folding to accommodate the presence of B7.1 in the fusion antibody. IgG3 also exhibits Fc mediated functions such as complement activation and Fc.gamma. binding (Morrison, S., In Vitro Antibodies: "Strategies for Production and Application," Annu Rev Immunol 10:239-65 (1992), which is hereby incorporated by reference). The B7.1 costimulatory ligand was chosen in preference to B7.2,

as Gajewski et al. and other investigators have suggested that B7.1 transduced tumors more successfully induce CTL activity, and protect against parental tumor challenge more effectively than tumors transduced with B7.2 (Matulonis, U. et al., "B7-1 is Superior to B7-2 Costimulation in the Induction and Maintenance of T Cell-Mediated Antileukemia Immunity. Further Evidence that B7-1 and B7-2 are Functionally Distinct," J Immunol 156:1126-31 (1996); Gajewski, T., et al., "Tumor Rejection Requires a CTLA4 Ligand Provided by the Host or Expressed on the Tumor: Superiority of B7-1 over B7-2 for Active Tumor Immunization," J Immunol 156:2909-17 (1996); Gajewski, T., "B7-1 but not B7-2 Efficiently Costimulates CD8+ T Lymphocytes in the P815 Tumor System in Vitro," J Immunol 156:465-72 (1996); Chamberlain, R. et al., "Costimulation Enhances the Active Immunotherapy Effect of Recombinant Anticancer Vaccines," Cancer Res 56:2832-6 (1996), which are hereby incorporated by reference). Although conflicting results with respect to Th1 versus Th2 differentiation have been reported using B7.1 and B7.2, results from several experimental systems suggest that B7.1 costimulation tends to favor differentiation along the Th1 pathway (Guinan, E. et al., "Pivotal Role of the B7:CD28 Pathway in Transplantation Tolerance and Tumor Immunity," Blood 84:3261-82 (1994); Freeman, G., et al., "B7-1 and B7-2 do not Deliver Identical Costimulatory Signals, Since B7-2 but not B7-1 Preferentially Costimulates the Initial Production of IL-4," Immunity 2:523-532 (1995); Greenfield, E. et al., "B7.2 Expressed by T Cells does not Include CD28-Mediated Costimulatory Activity but Retains CTLA4 Binding: Implications for Induction of Antitumor Immunity to T Cell Tumors," J Immunol 158:2025-34 (1997); Kuchroo, V. et al., "B7-1 and B7-2 Costimulatory Molecules Activate Differentially the Th1/Th2 Developmental Pathways: Application to Autoimmune Disease Therapy," Cell 80:707-18 (1995), which are hereby incorporated by reference). Therefore B7.1, rather than B7.2, was linked to an antitumor antibody in an effort to preferentially stimulate a Th1 mediated immune response.

Detail Description Paragraph:

[0159] The results indicate that B7.1 can be effectively linked to the amino terminus of the heavy chain of an anti-HER2/neu antibody, with retention of both antibody specificity and the B7.1 interaction with CD28. Binding to HER2/neu was demonstrated by flow cytometry, as well as IAsys biosensor studies, albeit at a lower affinity than that observed for the control her2.IgG3. Possible reasons for the observed decrease in affinity could be steric hindrance between the anti-HER2/neu variable and

DOCUMENT-IDENTIFIER: US 6525180 B1

**** See image for Certificate of Correction ****

TITLE: Antibodies to mammalian T cell surface antigen

Brief Summary Text (4):

It The activation of resting T cells is critical to most immune responses and allows these cells to exert their regulatory or effector capabilities. See Paul (ed; 1993) Fundamental Immunology 3d ed., Raven Press, N.Y. Increased adhesion between T cells and antigen presenting cells (APC) or other forms of primary stimuli, e.g., immobilized monoclonal antibodies (mAb), can potentiate the T-cell receptor signals. T-cell activation and T cell expansion depends upon engagement of the T-cell receptor (TCR) and co-stimulatory signals provided by accessory cells. See, e.g., Jenkins and Johnson (1993) Curr. Opin. Immunol. 5:361-367; Bierer and Hahn (1993) Semin. Immunol. 5:249-261; June, et al. (1990) Immunol. Today 11:211-216; and Jenkins (1994) Immunity 1:443-446. A major, and well-studied, co-stimulatory interaction for T cells involves either CD28 or CTLA-4 on T cells with either B7 or B70 (Jenkins (1994) Immunity 1:443-446). Recent studies on CD28 deficient mice (Shahinian, et al. (1993) Science 261:609-612; Green, et al. (1994) Immunity 1:501-508) and CTLA-4 immunoglobulin expressing transgenic mice (Ronchese, et al. (1994) J. Exp. Med. 179:809-817) have revealed deficiencies in some T-cell responses though these mice have normal primary immune responses and normal CTL responses to lymphocytic choriomeningitis virus and vesicular stomatitis virus. As a result, both these studies conclude that other co-stimulatory molecules must be supporting T-cell function. However, identification of these molecules which mediate distinct costimulatory signals has been difficult.

Brief Summary Text (64):

Further, the antibodies, including antigen binding fragments, of this invention can be potent antagonists that bind to the antigen and inhibit functional binding or inhibit the ability of a binding partner to elicit a biological response. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides so that when the antibody binds to antigen, a cell expressing it, e.g., on its surface, is killed. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker, and may effect drug targeting.

Brief Summary Text (106):

499E9, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, topical, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds.)

(1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Pa.; Avis, et al. (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications, Dekker, New York.; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Tablets, Dekker, New York; and Lieberman, et al. (eds.) (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems, Dekker, New York. The therapy of this invention may be combined with or used in association with other agents, e.g., other modulators of T cell activation, e.g., CD40, CD40 ligand, CD28, CTLA-4, B7, B70, SLAM, T cell receptor signaling entities, or their respective antagonists.

DOCUMENT-IDENTIFIER: US 6512095 B2

TITLE: Molecules designated B7L-1

Brief Summary Text (5):

B7-1 also interacts with the T cell CTLA4 receptor. Its signaling is complex, but one component provides a negative feedback signal, causing the T cell to attenuate the CD28 signal. In the absence of this signal for a long period of time, rampant T cell proliferation and effector cell activation continues. However, shorter term intervention can be beneficial by leading to a more vigorous immune response. For example, when the interaction of B7-1 (and B7-2) is blocked with antibodies to CTLA4 increased rejection of tumors has been found. When this feedback regulation malfunctions, autoimmune diseases and lymphoproliferation (refs) can result. For example, when the CTLA4 and B7-1 interaction is blocked with a soluble CTLA4Ig, allograft tolerance and resistance to autoimmune diseases have been observed.

Brief Summary Text (9):

Clearly, costimulatory signaling through T cell surface receptors plays an important role in maintaining balance in the immune system. Systems with a predominance of activatory signals, such as the costimulatory signaling between CD28 and B7-1, can lead to autoimmunity and inflammation. Immune systems with a predominance of inhibitory signals, such as the costimulatory signaling between CTLA4 and are less able to challenge infected cells or cancer cells. Isolating new molecules involved in costimulatory signaling is highly desirable for studying the biological signal(s) transduced via the receptor. Additionally, identifying such molecules provides a means of regulating and treating diseased states associated with autoimmunity, inflammation and infection. For example, engaging a molecule that stimulates inhibitory or negative signaling with an agonistic antibody or signaling partner can be used to downregulate a cell function in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present. On the other hand, using an antagonistic antibody specific for a molecule that stimulates negative signaling, or using a soluble form of the molecule to block signaling, can activate the specific immune function in disease states associated with suppressed immune function. Conversely, engaging a molecule that stimulates positive signaling with an agonistic antibody can be used to upregulate the effect of that molecule's signaling.

Detailed Description Text (48):

As discussed above, when various tissues were analyzed for mRNA for B7L-1, transcripts were detected in human bone marrow derived CD34+ derived dendritic cells and peripheral blood derived dendritic cells, B cells after stimulation with CD40L, brain and mouse splenic dendritic cells CD40L stimulated splenic B cells and brain. Because of the restricted expression pattern of B7L-1, antibodies to B7L-1 can be used to identify, isolate, and purify potent antigen presenting cells, including dendritic cells and CD40 ligand activated B cells. Additionally, the presence and level of mRNA for B7L-1 can be exploited to determine the purity of bone marrow derived and blood derived dendritic cell preparations. Other uses of antibodies to B7L-1 molecules include targeting antigens to myeloid dendritic cells or eliminating myeloid dendritic cells with anti-B7L-1 antibody mediated depletion or with an conjugate of a toxin and the antibody.

Detailed Description Text (50):

One embodiment of the present invention is directed to a method of treating disorders mediated by the interaction of B7L-1 and a binding partner and involves administering B7L-1 to a mammal having the disorder. B7L-1 polypeptides of the

invention can be formulated according to known methods used to prepare pharmaceutically useful compositions. B7L-1 can be combined in admixture, either as the sole active material or with other known active materials, with pharmaceutically pharmaceutically suitable diluents (e.g., Tris-HCl, acetate, phosphate), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), emulsifiers, solubilizers, adjuvants and/or carriers. Suitable carriers and their formulations are described in Remington's Pharmaceutical Sciences, 16th ed. 1980, Mack Publishing Publishing Co. In addition, such compositions can contain B7L-1 complexed with polyethylene glycol (PEG), metal ions, or incorporated into polymeric compounds such such as polyacetic acid, polyglycolic acid, hydrogels, etc., or incorporated into liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts or spheroblasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance clearance of B7L-1. B7L-1 can also be conjugated to antibodies against tissue-specific receptors, ligands or antigens, or coupled to ligands of tissue-specific receptors. For tumor cells on which LDCAM is found, B7L-1 may be conjugated to a toxin whereby B7L-1 is used to deliver the toxin to the specific cell site.

Detailed Description Text (50):

The present invention is further intended to include derivatives of antibodies or fragments thereof which retain a desired functional property, e.g., the ability to inhibit an interaction between gc chain and a gc chain ligand. Antibody derivatives include chimeric molecules, humanized molecules, molecules with reduced effector functions, bispecific molecules, and conjugates of antibodies or antibody portions with toxins or radionuclides. An antibody, or fragment thereof, produced in a non-human subject can be recognized to varying degrees as foreign when the antibody is administered into a human subject and an immune response against the antibody may be generated in the subject. One approach for minimizing or eliminating this problem is to produce chimeric, humanized, or primatized antibody derivatives, i.e., antibody molecules comprising portions which are derived from non-human antibodies (e.g., derived from mice or monkeys) and portions which are derived from human antibodies. Chimeric antibody molecules can include, for example, the variable region from an antibody of a mouse, rat or other species, with human constant regions. a variety of approaches for making chimeric antibodies have been described. (See, for example, Morrison et al., Proc. Natl. Acad. Sci. U.S.A. 81,6851 (1985); Takeda et al., Nature 314, 452 (1985), Cabilly et al., U.S. Pat. No. 4,816,567; Boss et al., U.S. Pat. No. 4,816,397; Tanaguchi et al., EP 171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B.) In a further modification, humanized antibodies have only the hypervariable domains of the variable region of non-human origin and have other parts of the variable region of the antibody, especially the conserved framework regions of the antigen-binding, domain, of human origin. Such humanized antibodies can be made by any of several techniques known in the art, (e.g., Teng et al., Proc. Natl. Acad. Sci. U.S.A. 80, 7308-7312 (1983); Olsson et al., Meth. Enzymol., 92, 3-16 (1982)), and are preferably made according to the teaching of PCT Publication WO 92/06193 or EP 0239400. Humanized antibodies can be commercially produced by, for example, Scotgen Limited, 2 Holly Road, Twickenham, Middlesex, Great Britain.

Detailed Description Text (133):

In this embodiment of the invention, unresponsiveness of a T cell to an antigen is maintained by contacting the T cell with an agent, such as a gc chain blocking antibody, which inhibits stimulation of the T cell through gc chain-encompassing cytokine receptors. Agents which inhibit stimulation by binding to gc chain may result in complete or partial inhibition, so long as it is sufficient to maintain T cell unresponsiveness as defined herein. In one embodiment of the invention, T cell unresponsiveness is maintained to an antigen on an allogeneic or xenogeneic cell. Accordingly, the method of the invention can be used to treat a subject who is a recipient of the allogeneic or xenogeneic cell, for example an organ transplant recipient, and is useful for inhibiting either rejection of transplanted tissue or graft vs. host disease in a subject. In another embodiment of the invention, T cell unresponsiveness is maintained to an autoantigen or to an allergen. Accordingly, the method of the invention can be used to treat a subject suffering from an autoimmune or an allergic disease, and is useful for alleviating the symptoms of those disorders associated with an inappropriate or undesired immune response. The gc chain blocking agent employed to maintain T cell unresponsiveness in these therapeutic situations may be administered subsequent to application of the agent used to induce T cell unresponsiveness. Where the agent used to induce T cell unresponsiveness is an agent other than a gc chain blocking antibody, such as CTLA-4 Ig, the gc chain blocking agent can be administered simultaneously with the inducing agent.

PGPUB-DOCUMENT-NUMBER: 20020004227
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004227 A1

TITLE: Method for making monoclonal antibodies and cross-reactive antibodies obtainable by the method

PUBLICATION-DATE: January 10, 2002

US-CL-CURRENT: 435/69.1; 435/325, 530/388.22, 536/23.5

APPL-NO: 09/ 828739 [PALM]
DATE FILED: April 9, 2001

RELATED-US-APPL-DATA:

Application 09/828739 is a division-of US application 09/329633, filed June 10, 1999, US Patent No. 6252050

Application is a non-provisional-of-provisional application 60/089253, filed June 12, 1998,

RELATED APPLICATION

[0001] This is a divisional of non-provisional application Ser. No. 09/329,633 filed Jun. 10, 1999 which claims priority under 35 USC 119(e) to provisional application Ser. No. 60/089,253 filed Jun. 12, 1998, the contents of which are incorporated herein by reference.

DOCUMENT-IDENTIFIER: US 20020004227 A1

TITLE: Method for making monoclonal antibodies and cross-reactive antibodies obtainable by the method

Detail Description Paragraph:

[0093] Preferred molecular targets for antibodies encompassed by the present invention include CD proteins such as CD3, CD4, CD8, CD19, CD20 and CD34; members of the ErbB receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor; cell adhesion molecules such as LFA-1, Mac1, p150.95, VLA-4, ICAM-1, VCAM and .alpha.v/.beta.3 integrin including either .alpha. or .beta. subunits thereof (e.g. anti-CD11a, anti-CD18 or anti-CD11b antibodies); growth factors such as VEGF; IgE; blood group antigens; flk2/flt3 receptor; obesity (OB) receptor; mpl receptor; CTLA-4; protein C; an Apo-2L receptor such as Apo-2, DR4, DcR1 and DcR2; and variants and/or fragments of the above-identified molecules etc.

Detail Description Paragraph:

[0140] The invention also pertains to immunoconjugates comprising the antibody described herein conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g. an enzymatically active toxin of bacterial, fungal, plant or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

First Hit

L6: Entry 80 of 125

File: PGPB

Jul 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020086014
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020086014 A1

TITLE: Human CTLA-4 antibodies and their uses

PUBLICATION-DATE: July 4, 2002

US-CL-CURRENT: 424/144.1; 424/146.1, 530/388.26

APPL-NO: 09/ 948939 [PALM]
DATE FILED: September 7, 2001

RELATED-US-APPL-DATA:

Application 09/948939 is a continuation-in-part-of US application 09/644668, filed August 24, 2000, PENDING
Application is a non-provisional-of-provisional application 60/150452, filed August 24, 1999,

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application Ser. No. 60/150,452, the disclosure of which is incorporated herein in its entirety.

PGPUB-DOCUMENT-NUMBER: 20020160000
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020160000 A1

TITLE: PD-1, a receptor for B7-4, and uses therefor

PUBLICATION-DATE: October 31, 2002

US-CL-CURRENT: 424/144.1; 424/93.7

APPL-NO: 10/ 068215 [PALM]
DATE FILED: February 6, 2002

RELATED-US-APPL-DATA:

Application 10/068215 is a division-of US application 09/645069, filed August 23, 2000, PENDING

Application is a non-provisional-of-provisional application 60/150390, filed August 23, 1999,

Application is a non-provisional-of-provisional application 60/164897, filed November 10, 1999,

RELATED APPLICATIONS

[0001] This claims priority to U.S. Ser. No. 60/150,390 filed on Aug. 23, 1999. This application also claims priority to U.S. Ser. No. 60/164,897, filed on Nov. 10, 1999. Both of these applications are incorporated herein in their entirety by this reference.

L6: Entry 75 of 125

File: PGPB

Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020142000

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020142000 A1

TITLE: Anti-CD3 immunotoxins and therapeutic uses therefor

PUBLICATION-DATE: October 3, 2002

US-CL-CURRENT: 424/183.1; 530/387.3, 530/388.75

APPL-NO: 09/ 480236 [PALM]

DATE FILED: January 10, 2000

CONTINUED PROSECUTION APPLICATION: This is a publication of a continued prosecution application (CPA) filed under 37 CFR 1.53(d).

PGPUB-DOCUMENT-NUMBER: 20020164686
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020164686 A1

TITLE: Molecules designated B7L-1

PUBLICATION-DATE: November 7, 2002

US-CL-CURRENT: 435/69.1; 435/320.1, 530/350, 536/23.5

APPL-NO: 09/ 778510 [PALM]
DATE FILED: February 6, 2001

RELATED-US-APPL-DATA:

Application 09/778510 is a continuation-of US application PC/T/US99/17906, filed August 5, 1999, UNKNOWN

Application is a non-provisional-of-provisional application 60/095663, filed August 7, 1998,